CANCERQUEST

A Closer Look: p53

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Abnormal p53 and Cancer Development

A cell lacking functional p53 may or may not become cancerous, and correspondingly, a cell with normal p53 function may eventually lead to the formation of a cancerous growth. As discussed in the section on Genetic Change, to become cancerous, several different changes to the DNA of a cell must occur. One of the functions of p53 is to monitor the status of the cell's DNA. Along with a host of additional proteins, p53 helps to recognize and effect repairs to damaged DNA. The responses to damaged DNA include repair, cessation of cell division and cell death. Damage to the *p53* gene does increase the likelihood of cancer development. Remember that since p53 is a tumor suppressor, both copies of the gene must be inactivated in order to see the full effects. There are several ways in which p53 can be inactivated:

Mutations
Alterations in the *p53* gene have have several different effects on the activity of the gene, depending on the location of the alteration.

1. Mutations may occur in regulatory regions. These portions of of the gene control how often, and when, the gene is transcribed (this region is called the promoter). A mutation in the promoter region can result in a decrease or absence of p53 in the cell.

2. Mutations that occur in the protein coding region of the gene can impact the expression of the gene (or activity of the protein) in several ways:

   - A decrease in the activity of p53 as a transcription factor. The expression of the target genes of p53 that would be affected include *p21* (a protein involved cell cycle regulation), *Bax* (a protein involved in the induction of apoptosis), and thrombospondin-1(an angiogenesis inhibitor).
   - A change in p53 that makes it more susceptible to degradation. If the p53 proteins in the cell are being degraded at a higher-than-normal rate they will not be able to perform their functions as tumor suppressors.

Viral Inactivation
One of the functions of p53 is in 'guarding' the genome. Infection with viruses introduces foreign DNA into cells. p53, along with other proteins, is responsible for the cell's response to the presence of foreign DNA. Again, the responses include shutting down cell division and cell death. To avoid these responses, several different viruses have evolved ways of inactivating the p53 protein. An example of this is Simian Virus 40 (SV40) Upon infection with SV40, viral proteins are produced within the cell cytoplasm. One of the proteins produced is termed the Large T antigen. A function of this protein is the binding and inactivation the p53 protein. Other viruses such as Hepatitis and Human Papillomavirus produce similar proteins.

The elimination of functional p53 from the cell clears the way for cell division even in the presence of DNA damage. In the absence of p53, genetic instability as evidenced by increased muations and aneuploidy are likely to increase. The increase in genetic damage leads to the accumulation of defective tumor suppressors and oncogenes.

Genes and Cancer

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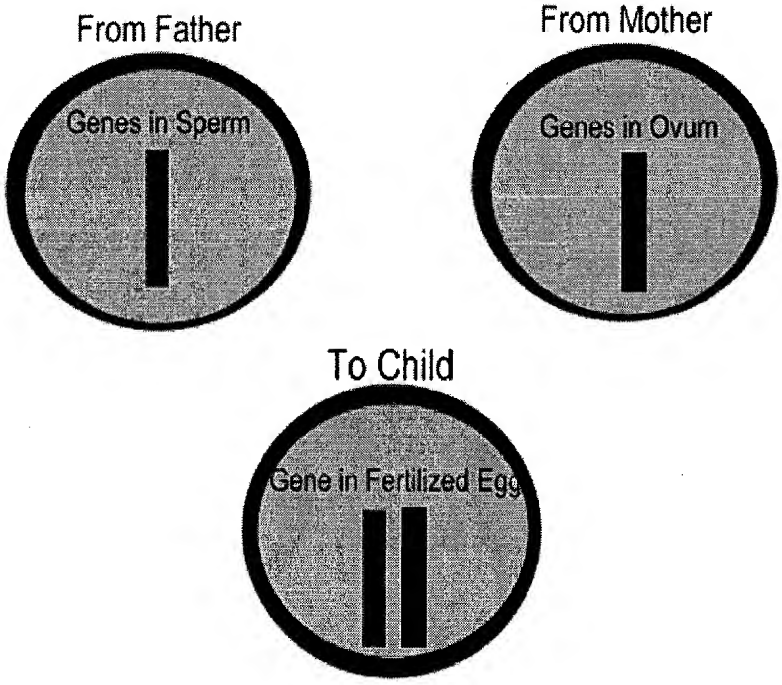
What are genes?

If we look at life as a book, Genes are the basic alphabet of this book. They determine the make of the contents, the messages and meanings of our lives. Genes are very small molecules in our cells, which determine almost everything in our body. All of us, one day, were just one cell, a fertilized ovum. One sperm cell from our father joined with one ovum from our mother, merging their genes and forming one cell. From there on, the cells divided and gradually formed various tissues and organs of our body.

Each Sperm and Ovum carry one copy of our parents' genetic map. The genes were then merged and passed on to us. And now, each cell of your body contains genetic information from both our parents.



The circles indicate the cells and the red and green columns indicate the complex of our genes within the cells. Each and every cell of our body contains same complex set of genes, 1/2 from our mother and 1/2 from our father.

Our parents inherited their genes from their parents, and the grand-parents from their great-grant parents and so on. This means that each part of our genes may belong to a grand parent, great grand parent or our parents,--and if some one had a bad **gene** a few generations ago, we may harbor it, -- generations later.

Our genes are clumped together in 23 pairs of chromosomes. Each chromosome contains genes from both parents. Simply, if you imagine the red and green columns in above picture as one chromosome, we have 23 pairs of Red and Green in each cell of our body.

Genes and **Cancers**:

With advancements in technology, we can now detect certain bad genes inside the cells. These bad genes that are known to be associated with causation of certain **cancers**. Unlike the genetic abnormalities of benign disorders, the genetic problems associated with **cancers** are for most part not understood and seem to be very complex and multiple in nature. Some of these abnormalities develop during the life of a cancer patient, as opposed to the hereditary nature of the benign genetic illnesses. Our current understanding about genes and their role in cancer divides them into two important categories of genes which are involved in the process of cancer development and progression:

Tumor Suppressor Genes: Our cells have variety of genes, some of which control their growth These genes are important part of our genetic makeup and they regulate growth and multiplication of the cells. As a result they can prevent **cancers** from happening. If something goes wrong with these genes, and if they don't function properly, cells may grow without a contol and cause cancer.

Example of these genes are:

RB **gene**; if this genes goes bad, it can lead to the development of Retinobalstoma, Bone, Breast, Lung, Prostate, Bladder and other **cancers**.

p53 gene; ***p53 suppresser gene*** can arrest replication of cells with damaged genes until normal repair process has taken place. If cells with damaged genes grow and replicate, they may result in a cancer. ***p53 gene*** suppresses the growth of such cells. If this genes goes bad, it can lead to the development of Breast, Colon, Leukemia, soft tissue sarcomas, and many other **cancers**.

APC **gene**; if this genes goes bad, it can lead to the development of Colon, Pancreas and Stomach **cancers**.

BRCA1; located in chromosome 17, if this genes goes bad, it can be associated with a very high risk of developing Breast cancer.

BRCA2; located in chromosome 13, if this genes goes bad, it can be associated with a very high risk of developing Breast cancer.

Oncogenes: These are among essential components of normal genes within the cells and if for some reason activated, they can eventually cause a cancer. These genes regulate normal growth of cells. More than 100 Oncogenes have been identified and associated with some form of cancer. What is unknown is "what activates these Oncogenes and what happens after they are activated?" External factors, radiation, certain chemicals may cause activation of Oncogenes and result in a cancer. These genes stimulate cell growth. On occasions, these genes can be overactive and cause rapid cell growth and cause a cancer. Example of these genes are:

MYC genes; which can result in Lymphomas

RAF genes; which can result in Stomach cancer

TRK genes; which can result in Thyroid cancer

Gene therapy

Cancer Genetic issues

Why to test?	Genes and Cancer	Available Tests
Breast Cancer	Ovarian Cancer	Colon and Rectal Cancer
Rare **Cancers**	Cancer Syndromes	Who needs to be tested?
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Family Issues		Other Issues

Website created and managed by M. Hossein Tirgan, M.D.

1: Proc Natl Acad Sci U S A. 1994 Jan 4;91(1):360-4.

UV and skin cancer: specific p53 gene mutation in norma as a biologically relevant exposure measurement.

Nakazawa H, English D, Randell PL, Nakazawa K, Martel N, Arm BK, Yamasaki H.

International Agency for Research on Cancer, Lyon, France.

Many human skin tumors contain mutated p53 genes that probat result from UV exposure. To investigate the link between UV e: and p53 gene mutation, we developed two methods to detect presumptive UV-specific p53 gene mutations in UV-exposed nc skin. The methods are based on mutant allele-specific PCRs anc chain reactions and designed to detect CC to TT mutations at cc 245 and 247/248, using 10 micrograms of DNA samples. These mutations in the p53 gene have been reported in skin tumors. C(mutations in the p53 gene were detected in cultured human skin only after UV irradiation, and the mutation frequency increased increasing UV dose. Seventeen of 23 samples of normal skin fro exposed sites (74%) on Australian skin cancer patients containe TT mutations in one or both of codons 245 and 247/248 of the p gene, and only 1 of 20 samples from non-sun-exposed sites (5% harbored the mutation. None of 15 biopsies of normal skin from sun-exposed or intermittently exposed sites on volunteers livin; France carried such mutations. Our results suggest that specific gene mutations associated with human skin cancer are induced i normal skin by solar UV radiation. Measurement of these mutati be useful as a biologically relevant measure of UV exposure in l and as a possible predictor of risk for skin cancer.

PMID: 8278394 [PubMed]

Recommendations on Predictive Testing for Germ Line p53 Mutations Among Cancer-Prone Individuals

COMMENTARY

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Almost every form of cancer in humans has been reported to aggregate in families (1,2). These familial clusters can be due to inheritance of a mutated cancersusceptibility gene, though other explanations include chance association and shared exposures to environmental carcinogens (3). In recent years, the chromosomal locations of some cancerpredisposing genes have been mapped by the new techniques of molecular genetics. A few have been identified, including the hereditary retinoblastoma (Rb) gene, WT1 gene for Wilms' tumor, neurofibromatosis type I gene, the APC gene of familial polyposis coli, and the p53 gene in **LiFraumeni syndrome** (4).

The work of the Human Genome Project (5) will soon lead to the identification of many more genes for hereditary diseases, including cancer. The proper use of genetic data on populations and individuals is a matter of growing concern. Some issues, such as autonomy, confidentiality, and nondiscrimination, are generic to testing for any heritable disease. These broader questions have been the subject of scholarly treatises, position papers, and legislation (6,10). Other issues are disease specific and determined by age at onset, disease severity, availability of treatment, mendelian inheritance pattern, and gene penetrance and expressivity (11). To date, discussions on testing for inherited mutations in cancer-susceptibility genes have been limited, perhaps because the cancers due to these mutations are rare (retinoblastoma and Wilms' tumor) or are preceded by distinctive clinical manifestations (neurofibromatosis and familial adenomatous polyposis).

Recent reports of germ line p53 mutations in families with **LiFraumeni syndrome** have raised the possibility of testing at-risk relatives who have not had cancer (12,13). This **syndrome** is an autosomal dominant disorder that predisposes individuals to multiple forms of cancer and that might

serve as a paradigm for future testing for a variety of sitespecific cancer susceptibility genes (1215). Two workshops, sponsored by the National Cancer Institute and the National Center for Human Genome Research, were held in 1991 to consider recommendations for p53 testing (16). The discussions focused on predictive testing, which for present purposes is the use of molecular genetic assays to detect inherited cancerpredisposing mutations in clinically healthy individuals. Predictive testing differs substantially from surveys of cancer patients for germ line p53 mutations that might explain the cause of cancers that have already developed. The participants in the workshops were from diverse fields of study, including clinical medicine, laboratory science, epidemiology and biostatistics, medical ethics, law, psychology, and cancer control. The sessions were informal and interdisciplinary. Participants shared their opinions and experiences and were not representing the positions of any governmental, voluntary, or private agency. Presentations and discussions covered several broad areas: 1) **LiFraumeni syndrome** and its relationship to germ line p53 mutations, 2) ethical considerations in predictive testing for germ line p53 mutations, 3) patient selection and the status of laboratory techniques for telling, 4) structure and components of pilot testing programs, and 5) opportunities for interventions and evaluation of the pilot testing activities. Recommendations were prepared primarily by participants who volunteered to serve on subcommittees responsible for distilling the consensus of the meetings. The recommendations were not voted upon and have **no** official status or authority. Rather, they are intended to call attention to an emerging issue and stimulate further discussion.

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Text

LiFraumeni Syndrome and Germ Line p53 Mutations

Background

This **syndrome** was initially recognized through clinical observations at the bedside, followed by epidemiology studies and searches for the defective gene in the laboratory (12,14). The **syndrome** is a clinical diagnosis based on the aggregation of two or more of the six forms of cancer currently known to occur in the **syndrome**. Individually, these cancers are clinically and histopathologically indistinguishable from their counterparts that arise in the general population. Approximately 50% of cancers in reported **LiFraumeni** families occur before 30 years of age (14). The most common childhood cancers have been softtissue sarcomas in the first 5 years of life and osteosarcomas in adolescence. Acute leukemia and brain tumors also occur throughout childhood and young adulthood, whereas the few adrenocortical carcinomas occur primarily in infancy. In young adults, premenopausal breast cancer is, by far, the most common neoplasm. Recent data suggest that gonadal germ cell tumors might be a seventh component of the **syndrome** and the possibility of additional component tumors cannot be excluded (15,16). Cancer patients in these families who survive the first neoplasm are prone to develop second cancers, particularly within the field of radiation therapy.

In 1990, five families with **LiFraumeni syndrome** were reported to show germ line mutations in the p53 gene (12). Subsequent studies have found germ line p53 mutations in some **LiFraumeni** families, but not in others (13,1720). The discordant results could be due in part to the failure to analyze the entire p53 gene. Another explanation is that the **syndrome** is genetically heterogeneous, with p53 mutations accounting for only a fraction of **LiFraumeni** families. Generally classified as a tumorsuppressor gene, p53 is the most common site of somatic mutations in human cancers (21). The p53 mutations appear to be an important change in the multistep process of carcinogenesis and, as germ line mutations, represent a first-hit in Knudson's twomutation model of hereditary cancer development (3). Germ line mutations in p53 tend to occur within the conserved regions of the gene and at codons that undergo somatic mutations in cancer cells. Problems arise in interpreting the functional importance of germ line p53 alterations at other codons. Linkage data on p53 mutations in **LiFraumeni** families are limited. Among **LiFraumeni** families with a germ line p53 mutation, the mutation has not segregated with cancer in at least one relative (13). In another family thought to have the clinical **syndrome**, evidence for linkage with the retinoblastoma gene was reported in an abstract (20). Clinically, the range of cancers in the **syndrome** remains to be defined.

Recommendations

1) **LiFraumeni syndrome** is a devastating autosomal dominant disorder of multiple cancers that are difficult to treat and often lethal. Cancer control through prevention and early detection should be pursued in affected families. Availability of a laboratory test to identify carriers is an important step toward achieving this goal.

2) Mutations in the tumor suppressor gene p53 are the most common acquired alterations in human cancers. Germ line p53 mutations in **LiFraumeni syndrome** and other rare cancer families can be considered a biomarker of increased risk for cancer development.

3) Current understanding of **LiFraumeni syndrome** and its association with germ line p53 mutations is incomplete. Additional studies are needed of the cancer spectrum in the **syndrome**, the role of environmental carcinogens in cancer development among family members, possible genetic heterogeneity identifiable by linkage analysis and other methods, agespecific penetrance of the mutant gene(s), and rare p53 polymorphisms that might be mistaken for functional mutations.

4) The deficiencies identified in recommendation 3 do not preclude predictive testing for germ line p53 mutations in selected cancerfree subjects. Inherited mutations at sites of somatic p53 mutations probably convey a substantial increase in cancer risk. Knowledge of the inherited change can be useful to patients and their physicians.

Ethical Issues in Predictive Testing in LiFraumeni Families

Background

Predictive testing for p53 mutations should be guided by the four ethical principles of respect: for autonomy, beneficence, confidentiality, and justice (69,22). Autonomy recognizes freedom from coercion, full understanding of the implications of an action, and respect for an individual's right to decide about something which may have a profound effect on his or her life. Beneficence, a fundamental principle of medicine, is summarized by the phrase "first do **no** harm." Beneficence underlies the responsibility of investigators and counselors to avoid harming persons who are not equipped to deal with predictive testing results. Confidentiality requires attention to avoid inadvertent disclosure of information to third parties. Finally, justice implies fairness, which includes access to health care and freedom from discrimination based on predictive testing results. These ethical principles are applicable to p53 predictive testing in members of families with **LiFraumeni syndrome**.

Recommendations

1) All persons chosen for testing on the basis of their family histories should be given current, relevant information on the test to make an informed voluntary decision. They should be provided with the highest quality of information and counseling available.

2) The right to decide to undergo testing rests solely with the individual concerned. Under **no** circumstances should any counselor communicate information concerning the test and its results to third parties without consent of either the person tested or the parents/guardian in the case of a minor child or mentally incompetent adult.

3) Cancers occur with high frequency among children in **LiFraumeni** families, and testing these children (rather than delaying it until young adulthood) is recommended, with the goal of reducing cancer morbidity and mortality. As children mature, it is appropriate to consider their assent or dissent to testing as well as their parents' permission. Parents and investigators should develop a plan on the timing and person(s) to convey test results to children.

4) Whereas early detection of disorders such as Huntington's disease, for which there is **no** treatment, does not improve survival, early cancer detection can substantially improve the likelihood of **cure**. The decision to inform (or not to inform) health care providers of test results should be discussed fully with the individual before and after testing.

5) Each participant should be able to take the test regardless of his or her financial means.

6) A participant can withdraw from the testing program at any time before the reporting of the test result. Thereafter, the subject should be encouraged to remain under followup observation so that support services can be provided and the impact of testing can be evaluated.

7) Predictive testing for germ line p53 mutations should be initiated only after counseling and support services are established. It may also be

advisable to postpone testing applicants with evidence of a serious current psychiatric condition.

8) Explicit compliance with ethical principles of genetic testing should help minimize psychological, social, economic, and other harm that might result from predictive p53 testing.

Patient Selection and Laboratory Techniques

Background

Predictive testing of healthy persons is distinct from surveys of cancer patients for germ line p53 mutations (16). Predictive testing, as envisioned, is a sequel to these survey studies. The purpose of surveys among cancer patients is to identify the small subset whose disease might be attributable in part to a germ line p53 mutation. The very low prevalence of germ line p53 mutations in the general population precludes direct study of unselected cancerfree subjects. Even among cancer patients, the prevalence of germ line p53 mutations is a fraction of 1%. Predictive testing does not pose major technical problems when the subjects are limited to close relatives of cancer patients found on surveys to have a germ line p53 mutation. Testing of these relatives involves only examination for the mutation previously detected in a family member with cancer. Current methodologies involve use of polymerase chain reaction (PCR) to amplify the codon(s) of interest. Although PCR artifacts or contamination can occur, both should be detectable by repeat analyses of additional specimens. In marked contrast, surveys for germ line p53 mutations potentially require analyses of the entire gene, which is approximately 20 kilobases with 11 exons that encode a protein with 393 amino acids (12). Searches for germ line p53 mutations have largely been limited to exons 59. These exons contain highly conserved regions with several codons that are preferred sites for somatic mutations. Surveys for germ line p53 mutations, most of which are point mutations, are laborious and costly. Consequently, several gel electrophoresis methods have been used to screen blood specimens for p53 mutations (12). The major advantage of screening methods, such as single strand conformational polymorphism and constant denaturing gel electrophoresis, is their relative simplicity. Unfortunately, the sensitivity and specificity of these gel methods in p53 screening are unknown, but both falsepositive results and falsenegative results have been encountered. When a shift in mobility of a DNA specimen is detected in the gel, the presence of a mutation needs to be established by gene sequencing.

Biostatistical issues also arise in surveys for germ line p53 mutations (16). The predictive power of a positive test for p53 is determined by three factors: 1) the prevalence of p53 mutations in the study population, 2) the sensitivity (probability of detecting a true positive) of the test, and 3) the specificity (probability of detecting a true negative) of the test. Even when sensitivity and specificity are very high (99%), the predictive power of a positive test is only 50% when the prevalence of p53 mutations in the survey population is 1%; i.e., only one half of those with a positive p53 test actually are cancerprone individuals. The power of the test is increased substantially by studying populations with high prevalence, preferably greater than 10%. In predictive testing of siblings and offspring of cancer patients with a germ line p53 mutation, the prevalence of mutation is as high as 50%. Available data suggest that the prevalence of this germinal mutation might be 0.01% in the general population, 0.1%1% among various cancer patients, and 5%10% among young patients with multiple primary cancers (16).

Recommendations

1) Predictive testing for germ line p53 mutations is technically feasible. It should be carried out in pilot research programs so that benefits and risks to participants can be determined.

2) Clear distinction is needed between predictive testing in healthy individuals and surveys of cancer patients for germ line p53 mutations. Surveys for germ line p53 mutations among select subgroups of cancer patients, particularly those in **LiFraumeni** families, should be encouraged as research activities. However, surveys using current laboratory techniques should be recognized as laborintensive endeavors that may yield both falsepositive and falsenegative results.

3) To be highly accurate, predictive testing should presently be offered only to close relatives of cancer patients whose mutant codon in the p53 gene has been identified through surveys of affected members of **LiFraumeni** families and other cancer patients. In **LiFraumeni** families without a

surviving cancer patient to study for a germ line p53 mutation, atrisk relatives can be tested after appropriate counseling on the limitations of testing.

4) All laboratories are expected to meet high standards of accuracy. Exchanges of blinded specimens among testing laboratories should help maintain quality control. Laboratory researchers must also work with counselors and other professionals providing the test service.

5) Predictive testing and counseling should be conducted in a research setting and should involve experts in oncology, psychiatry, psychology, genetic counseling, medical ethics, and medical and molecular genetics. However, the DNA test center can be at a different site from the counseling center.

6) Predictive p53 testing of the general population outside defined research settings is more likely to be harmful than beneficial. It is not recommended.

7) Research is needed to develop simpler, cheaper, and more accurate methods for use in surveys for germ line p53 mutations among cancer patients. In seeking p53 mutations, one should be cautious in interpreting changes at codons not previously found in human cancers because some of these changes might be polymorphisms.

Structure and Components of Pilot Testing Programs

Background

The most extensive experience with predictive testing relates to Huntington's disease, an autosomal dominant trait with 100% penetrance, variable age of onset in adulthood, and no available treatment (7,11,23). Initial surveys indicated that as many as 80% of individuals at risk said they wanted the test for purposes of planning for the future, relieving anxiety, and making childbearing decisions. A much smaller fraction has actually been tested. To date, the adverse effects of disclosure on the wellbeing of the patients have been modest. They include depression, anecdotal reports of job loss, and psychiatric hospitalization of a few patients. These experiences with Huntington's disease have relevance to the design of p53 testing programs. However, the two disorders differ in clinical spectrum, age at onset, course, and opportunities for prevention and therapy. Huntington's disease carriers are identified by linkage analysis because the gene has not been isolated. Although the experience with Huntington's disease testing indicates little change in lifestyle of patients after testing, the impact of testing might have been minimized by the support provided for participants. We cannot assume that the impact of testing for germ line p53 mutations in less supportive environments would also have minimal adverse effects. Predictive testing of children, as proposed herein, has received relatively little attention in the genetics literature (24). Testing of apparently healthy children for a trait that might stigmatize them for a lifetime requires adequate protections and safeguards, particularly informed consent.

Recommendations

1) Protocols and informed consent processes should be developed and should be approved by an institutional human protection committee before any predictive testing is initiated.

2) Test centers are encouraged to establish an outside advisory committee of medical genetics professionals and other experts to advise and monitor the predictive testing program.

3) According to published federal research guidelines, predictive testing for germ line p53 mutations should be considered a procedure involving "minor increase over minimal risk" (25).

4) Testing should be offered to competent adults at their request, subject to their willingness to participate in a longterm program of genetic counseling and psychological evaluation.

5) With regard to children, parents have a legal right to act as proxies. The decision to test children must be based on concern for the welfare of the child to be tested, particularly the potential impact of test results on the child's life.

6) Since our knowledge of the impact of predictive testing on children is limited, an additional safeguard might be temporary postponement of the testing of minors until shortterm effects of predictive testing of adults in their families are known.

7) If they become part of the group to be examined, atrisk children age 7 and older should be given ageappropriate explanations of their potential participation in a predictive testing research program. They should be asked for their decision, and dissent of adolescents should be strongly considered. In case of unresolvable disagreement between the minor and parents or legal guardians, the decision on testing should be handled on a casebycase basis, preferably with input from the outside advisory committee and institutional ethics committee (if available).

8) Before being tested, each candidate should provide a complete medical and family history, undergo a physical examination and perhaps laboratory tests, have baseline psychological testing, and receive genetic and psychological counseling. Counseling should encompass potential benefits and risks, including socioeconomic discrimination, psychological distress, family disruption, and higher insurance and medical expenses.

9) Participants should be given the option of having a partner to accompany him or her throughout the stages of testing. The issue of informing health care providers of test results should be determined before testing and should be reviewed at disclosure of the result.

10) The protocol for testing should specify procedures for delivery of results and followup, including psychological, social, and medical evaluation and support.

11) Prenatal testing should be restricted to situations in which one parent is known to have a germ line p53 mutation. Informed consent for couples requesting prenatal testing should include information about uncertainties regarding penetrance, expressivity, and age at onset. At a minimum, the potential of present and future opportunities for early detection, treatment, and chemoprevention should be discussed.

12) Cost of participation in testing needs to be addressed, particularly since equal access to testing should be fundamental to these programs.

13) For the moment, predictive testing should be considered investigational, and testing for purposes other than health care should be discouraged. Candidates for testing should be advised to examine their insurance status before disclosure of the results.

Interventions and Evaluation

Background

Data suggest that gene carriers in **LiFraumeni** families have a 50% likelihood of developing cancer by 30 years of age, as compared with a 1% likelihood in members of the general population (12). The frequency of cancer among carriers approaches 90% by 60-70 years of age. None of the component tumors in the **syndrome** has a high **cure** rate, with the exception of early breast cancer, rare germ cell tumors of the testis, and childhood acute lymphocytic leukemia. The prognosis of patients with the solid tumors in the **syndrome** generally improves with earlier stage at diagnosis. Among these tumors, however, only screening for breast cancer has been shown to reduce mortality (26). The reduction occurs primarily among screening data to breast cancers in young women in **LiFraumeni** families is uncertain. There are no proven methods of screening for cancers in children in the general population, though studies of neuroblastoma detection in neonates are in progress. There is precedent for case finding of exceptionally high-risk children, such as those with aniridia who are prone to Wilms' tumor (27,28). Routine screening procedures in p53 carriers

might include blood cell counts and perhaps radiographic studies, but the predictive power of the tests is unknown. Screening is further complicated by the wide spectrum of tumor types and sites in **LiFraumeni syndrome**. One option is not to perform any laboratory tests for early cancer. At the other extreme, periodic magnetic resonance imaging of multiple body sites might be advocated as the surveillance procedure of choice because no radiation is delivered and small lesions can be detected. The main drawbacks are the cost, an unknown falsepositive rate, and lack of availability of the study. The possibility of chemoprevention should be explored, although the agent of choice is uncertain (29). Given the marked loss of human potential that results from the death of a child, pilot research protocols for early intervention in p53 mutation carriers are justifiable. Because the effects of testing are unlikely to be known for many years, wellcoordinated, longterm studies are needed to assess outcomes.

Recommendations

1) An overall benefit of predictive p53 testing cannot be assumed and should be evaluated along with harmful effects in research protocols. Potential psychological, economic, and social benefits to those who test negative should be weighed against the increased distress to others who test positive.

2) The p53 carriers should be counseled to seek early medical attention for signs and symptoms of cancer, and their changes in patterns of utilization of health services should be evaluated.

3) Evaluation should be made of psychosocial effects, both beneficial and harmful, that result from predictive testing. Effect of support services to ameliorate harmful consequences should be monitored.

4) The p53 carriers should be counseled and urged to pursue a healthier lifestyle and diet, with avoidance of cigarette smoking, excess alcohol use, and exposures to other carcinogens; compliance should be evaluated.

5) Pilot chemoprevention research studies should be considered in p53 mutation carriers, such as a tamoxifen trial to prevent breast cancer.

6) Physicians of test subjects need to be educated about the extraordinary risk of cancer in p53 carriers, the need for confidentiality, and the importance of attention to complaints that might be attributed to cancer.

7) Because reduction in cancer morbidity and mortality will require many years to evaluate, test subjects should have long-term followup.

8) Evaluation of benefits and harm will be hampered by the limited numbers of eligible study subjects. Large effects, whether beneficial or harmful, might be detectable with as few as 1015 subjects. However, smaller effects are likely to require study of 100 or more subjects. Therefore, test centers should be encouraged to use protocols with some similar elements so that these results can be pooled to increase statistical power.

9) Registries should be established to collect data on **LiFraumeni** families and collate findings from p53 testing programs worldwide.

10) A national advisory group should be established to address issues, such as professional and public education, that are generic to predictive testing for mutations in cancer susceptibility genes.

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